Remarks

Claim amendments

Claims 15-17 are pending in the application. Claim 15, the only independent claim, has been amended to include the limitation "a plurality of a least 5 optical fiber bundles, each said bundle transmitting light to one of a plurality of at least 5 separate fluorescent detector entities." This limitation is fully supported by the specification, see p. 17 and Figure 4. Other stylistic changes to the claim have been made. In addition, following the examiner's most kind suggestion, the references to the various types of probes detected by the device have been removed as these were mere suggestions of utility and not claim limitations. No new matter has been added to the claim by the amendments. Therefore entry of the amendments is respectfully requested.

Claim rejections under 35 U.S.C. § 112

Claim 15 was rejected as indefinite for reciting "by at least 25 and preferably at least 30 nm." The Applicants have on file a claim reciting "by at least 25-30 nm." The discrepancy is now moot: the Applicants hereby amend the claim to recite "by at least 25 nm." The amended formulation is no longer subject to a §112 rejection.

Claim rejections under 35 U.S.C. §103

Claims 15-17 were rejected under §103(a) as being unpatentable over Bell and Ranford-Cartwright (2002) Trends in Parasitology, v.18(8), pp. 337-342, as evidenced by Wittwer et al. (1997) Biotechniques, v.22(1) pp. 176-181, in view of Hiratsuka et al. (2002) Clin. Biochem., v.35(1), pp. 35-40, Epstein et al. (2002) Anal. Chim. Acta, v.469, pp. 3-36 and Glazer et al., U.S. Patent No. 6,150,107. The rejection is respectfully traversed.

Briefly, the Applicants teach a real-time PCR instrument with at least five separate detectors and the same number of bundles of optical fibers simultaneously directing the full-spectrum light beam to each one of the detectors. (See Figure 4). None of the cited references teach the fiber bundles. Some references teach a single detector with a wheel having a series of wavelength filters placed in front of the detector. As the wheel rotates, the wavelengths are read ***sequentially*** not ***simultaneously*** as in the Applicants' invention. The remaining prior art devices use separate detectors so that all the wavelengths are read simultaneously. However, instead of ***fiber bundles***, the detectors receive light from a plurality of ***dichroic mirrors***. As explained in detail below, switching from dichroic mirrors to fiber bundles allows adding many more detectors and achieving much greater resolution of wavelengths.

Bell reference

The examiner stated that Bell (referred to as Ranford-Cartwright in the office action) teaches simultaneously scanning several samples and simultaneously detecting at least two differently labeled TaqMan probes. Bell also teaches the detection of SYBR® Green.

Bell is a user survey that does not explain how each of the surveyed devices works. In Table 1, Bell mentions "detection channels" without stating whether these are several detection entities or a single entity capable of detecting several dyes. Furthermore, Bell does not state whether the detection is simultaneous[1] or sequential. The Applicants reviewed the literature on each device cited by Bell and found that each device uses a ***single*** detector that performs ***sequential*** detection of wavelengths. In contrast, the Applicants' invention constitutes a ***plurality*** of detectors, performing ***simultaneous*** detection.

The first device cited by Bell, ABI PRISM® by Perkin Elmer (by Applied Biosystems), is shown on Exhibit 1, an excerpt from a user manual. A diagram on p. D-4 shows a single charge-coupled device (CCD)-array detector. A single grating splits the beam into separate wavelengths. As illustrated on p. D-5, the detector reads the entire spectrum of wavelengths and then uses a mathematical algorithm to parse out contributions of each dye. Clearly, the number of dyes that can be separated out from the same combined spectrum is limited. The illustration shows only three such dyes.

The Applicants' invention uses a different principle. There is no single device splitting the beam into multiple wavelengths. Instead, each one of the plurality of detector entity receives a complete beam transmitted by a bundle of optical fibers. Each entity has its own filter with a narrow range of wavelengths. The filter does not split the beam into multiple wavelengths but merely separates out a single desired range. This range is transmitted to the detector (see Figure 4). When emissions from several dyes are not combined in the first place, there is no need for mathematical analysis separating them. Therefore many more dyes may be used, including dyes with very close emission maxima.

The second device is the Light Cycler™ by Roche Molecular Diagnostics, shown on Exhibit 2, a page from the company's website. This device has separate detector entities, each detecting fluorescence of a particular wavelengths. The detectors receive light from a series of dichroic mirrors (mirrors that reflect some light but allow the remaining light to pass through). The set of dichroic mirrors is inferior to the fiber bundles because each successive detector receives less light. As discussed in more detail in the section devoted to the Wittwer reference,

dichroic mirrors are especially disadvantageous when the dyes being detected have very close or partially overlapping emission spectra. For each subsequent dye, a part of the spectrum will be cut out by the preceding dichroic mirror. Therefore the Light Cycler™ does not anticipate the Applicants' invention because it lacks an essential element of the invention: bundles of optical fibers that each deliver a full-spectrum beam to each detection entity.

The third device is iCycler™ iQ by Bio-Rad, shown on Exhibit 3, p. 3 of the instrument manual. The fourth device is Rotor-Gene™ by Corbett Research, shown on Exhibit 4, a page from the company's website. The fifth and final device is the Mx system by Stratagene, shown on Exhibit 5, p. 2-3 of the instrument manual. The four devices in this group share the same principle of operation. The signal is received by a single CCD or PMT detector with a filter disc placed in front of it. The disc rotates and sequentially allows each filtered wavelength to reach the detector. As explained above and shown on Figure 4, the Applicants' invention is capable of simultaneous detection of all desired wavelengths and does not use a rotating filter disc.

As the foregoing survey demonstrates, the devices disclosed in Bell are different from the Applicants' invention. Furthermore, the elements of the Applicants' invention may not be assembled from any combination of these prior art devices. None of the devices have a plurality of detector entities, each fed by a bundle of optical fibers and receiving a full-spectrum beam via the fibers.

Wittwer reference

The examiner stated that Wittwer teaches a single light source and different filters for SYBR® Green, fluorescein, rhodamine and Cy5™. Wittwer discloses three detector entities capable of simultaneously detecting at least three different dyes. However, Wittwer does not teach bundles of optical fibers delivering the same beam to the separate detectors. Instead, Wittwer uses dichroic mirrors to filter out the desired spectrum for each detector. Wittwer device operates under the same principle as the Light Cycler™ cited by Bell. Wittwer teaches:

> For three-color acquisition of fluorescein, rhodamine and Cy5, a 560-nm dichoric reflects fluorescein emissions, a 630-nm dichroic reflects rhodamine emissions and a 650-690-nm band-pass filter is used for Cy-5 collection.

See Wittwer, p. 178, ¶ 4. In contrast, the Applicants teach:

> The excitation and detection unit are connected by a multiple-leg fiber bundle. Emitted light from the reaction vessels (e.g. the glass capillaries) is homogeneously distributed using a lightpipe and is transmitted into six glass fiber bundles. These

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[1] Clearly, the detection is "simultaneous" to the extent that it takes place in the same tube during the same experiment. However, such detection can take place sequentially, when the one wavelength is read after another, or simultaneously, when all the wavelengths are read at once.

> bundles of 50 um single glass fibers transmit the light into each of the six detection channels.

See p. 17, lines 14-18. Further, Applicants emphasize that, "Moreover, [by use of the fiber bundles], the number of necessary dichroic mirrors is minimized." Id., lines 24-25. The use of mirrors limits the ability to detect multiple dyes with close emission spectra. When the emission spectra of the dyes overlap, each corresponding mirror will filter out a portion of the spectrum of each subsequent mirror, diminishing the signal from each subsequent probe. This problem does not exist in the Applicants' device, because each detector entity starts with a full-spectrum light beam.

For an invention to be obvious, all the claim limitations must be taught or suggested by the prior art. See MPEP 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (C.C.P.A. 1974). Nothing in the prior art teaches or suggests the use of fiber bundles to direct the complete-spectrum beam to separate detector entities in a real-time PCR device. Wittwer teaches splitting the wavelengths with dichroic mirrors ***before*** they reach the plurality of detectors. The devices cited by Bell teach filtering out wavelengths ***before*** they are sent to the detector one-by-one. Even if a person of ordinary skill were to combine Wittwer and Bell, the result would be a multi-detector device where the beam is split by dichroic mirrors or filters ***before*** traveling to the detectors. Nothing in the prior art suggests (1) bundles of optical fibers feeding a plurality of detector entities; and (2) transmitting the unsplit beam to the detector entities. Because of these two differences, the Applicants' redesign of the detection system is much more substantial than a mere substitution of a single known element for another known element. Admittedly, there was interest in designing a real-time PCR device able to detect more and more dyes. However, such motivation is not enough. The prior art must suggest the use of two new elements of the detection system and also predict that the new elements would work well in a real-time PCR device. Because no such suggestion or assurance of success can be found, an obviousness rejection over Wittwer and Bell may not be sustained. Reconsideration and withdrawal of the rejection are respectfully requested.

Hiratsuka, Glazer and Epstein references

The Applicants respectfully point out that Hiratsuka does not fill the gap in Bell and Wittwer with respect to "a plurality of a least 5 optical fiber bundles, each said bundle transmitting light to one of a plurality of at least 5 separate fluorescent detector entities." Although Hiratsuka teaches detecting five separate SNPs, this is done with a ***single dye***

combination. For all five probes, Hiratsuka uses the same FRET pair: LC Red 640 and FITC (see p. 37, section 2.4). Clearly, for a single wavelength emitted by this FRET pair, the instrument needs one, not five detectors.

Glazer teaches various fluorescent dyes, not the instruments used to detect them.

Finally, Epstein gives a user survey of various fluorescence-based nucleic acid detection techniques. Epstein shows schematic diagrams of several devices on Figures 11, 15 and 21. All the devices surveyed have a single detection entity and a single filter or a "filter wheel", suggesting that they employ the same principle as the devices surveyed by Bell.

In summary, neither Hiratsuka, Glazer, Epstein or their combination fills the gap in the teachings of Wittwer and Bell. These secondary references do not teach or suggest using a bundle of optical fibers delivering a full-spectrum beam to each one of several detectors. Therefore an obviousness rejection over Wittwer and Bell in view of Hiratsuka, Glazer and Epstein may not be sustained. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 16 and 17 depend upon claim 15 and therefore incorporate all the limitations of that claim. For the reasons presented in reference to claim 15, the obviousness rejection of the dependent claims should also be withdrawn.

Conclusion:

In view of the above, Applicants believe that all claims now pending in this Application are in condition for allowance. The Commissioner is authorized to charge the fee for a three-months extension of time to respond to the office action (large entity) to Deposit Account No. 50-0812. The Commissioner is further authorized to charge any fee deficiency, or credit any overpayment to the same account.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned directly at 510-814-2706.

Respectfully submitted,

Date: December 14, 2007

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